Cluster of atypical adult Guillain-Barré syndrome temporally associated with neurological illness due to EV-D68 in children, South Wales, United Kingdom, October 2015 to January 2016

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We report a cluster of atypical Guillain-Barré syndrome in 10 adults temporally related to a cluster of four children with acute flaccid paralysis, over a 3-month period in South Wales, United Kingdom. All adult cases were male, aged between 24 and 77 years. Seven had prominent facial diplegia at onset. Available electrophysiological studies showed axonal involvement in five adults. Seven reported various forms of respiratory disease before onset of neurological symptoms. The ages of children ranged from one to 13 years, three of the four were two years old or younger. Enterovirus testing is available for three children; two had evidence of enterovirus D68 infection in stool or respiratory samples. We describe the clinical features, epidemiology and state of current investigations for these unusual clusters of illness.

The event

In January 2016, an initial cluster of five cases of Guillain-Barré syndrome (GBS) in adult males was reported to Public Health Wales by neurologists at the University Hospital Wales in Cardiff. Unusually for GBS there was: prominent bilateral facial weakness (facial diplegia), evidence for axonal damage on nerve conduction studies rather than the more typical demyelinating pattern; atypical clinical onset of symptoms and atypical clinical progression. During the initial investigations, two cases of acute flaccid paralysis (AFP) in children from the same areas were identified.

Background

GBS is an acute inflammatory peripheral nerve disorder of which the commonest type is a demyelinating, ascending paralysis, accounting for around 90% of cases. There are rarer but recognised variants, including Miller Fisher syndrome (MFS), around 5% of GBS, which is typified by the triad of ophthalmoplegia, ataxia and areflexia; and acute motor axonal neuropathy (AMAN), 5% of GBS) in which an axonal rather than demyelinating pattern of nerve damage is seen and tendon reflexes can be paradoxically brisk [1].

GBS is considered to be an autoimmune disorder triggered by many recognised precipitants via molecular mimicry. There are multiple reports of AMAN clusters, most notably in Asia such as the northeast China outbreaks where an infectious agent has been suspected [2]. AMAN clusters in North America and Europe are much less common and the clinical pattern described by many probable cases here defy contemporary diagnostic categorisation [1].

There are several known infectious triggers for GBS. *Campylobacter* spp. is the most commonly reported prodromal infection, and has been associated with clusters of the axonal variants of GBS in China [3]. Influenza is also a known trigger [4]. More rarely other infectious caused by pathogens such as hepatitis A [5], *Mycoplasma pneumoniae* [6], *Acinetobacter baumannii* [7], cytomegalovirus [8] and Ebstein-Barr virus [9] have been associated with GBS and AMAN syndrome. Recently, hepatitis E virus has been suggested as a possible common trigger for GBS [10], and the emerging Zika and West Nile viruses have also been linked to GBS [11,12].

AFP is a clinical presentation, rather than diagnosis, with rapid onset of weakness of one or more limbs,

Figure 1

Child and adult cases by local authority, adult cluster of atypical Guillain-Barré syndrome and child cluster of acute flaccid paralysis, South Wales, United Kingdom, October 2015–January 2016 (n = 14)

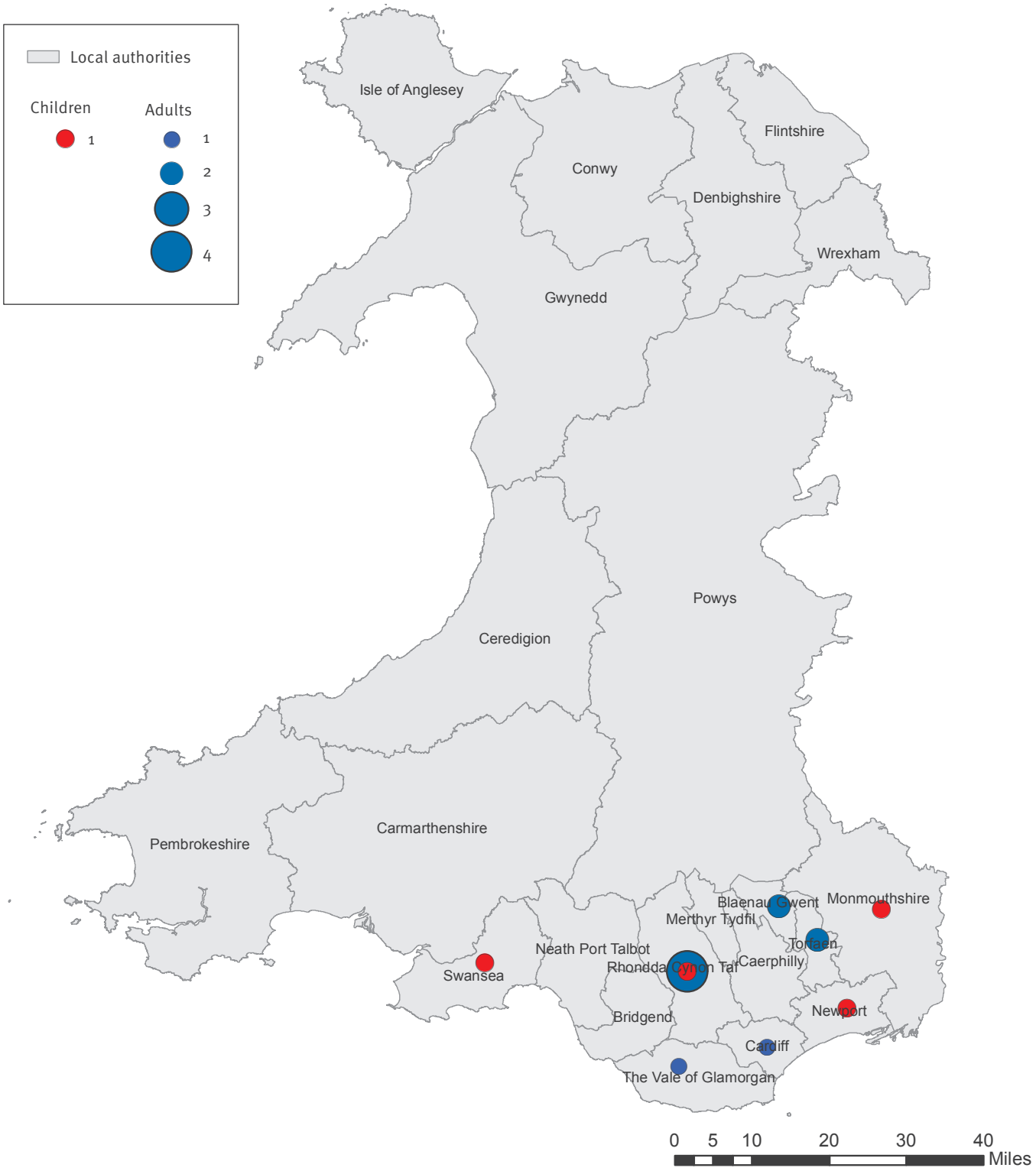

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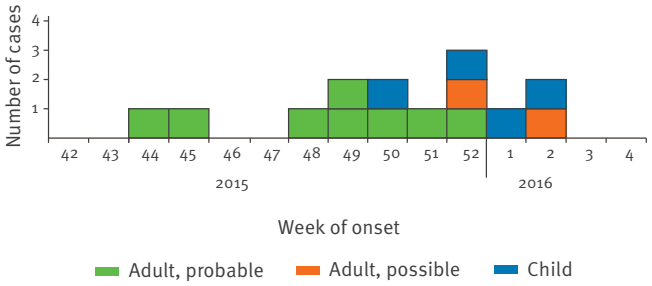
Figure 2

Weeks of onset of paralysis for adult and child cases, by case category, adult cluster of atypical Guillain-Barré Syndrome and child cluster of acute flaccid paralysis, South Wales, United Kingdom, October 2015–January 2016 (n = 14)



sometimes associated with weakness of muscles involved in swallowing and respiration, and progression over days and weeks. GBS is one of the differential diagnoses for AFP [13]. Acute poliomyelitis is another, with AFP surveillance an important part of the surveillance for polio. More recently, enterovirus D-68 (EV-D68) has been found to cause an illness presenting with AFP, with radiological evidence of an acute myelitis [14].

The population included in this paper covers the counties of Vale of Glamorgan, Rhondda Cynon Taff, Merthyr Tydfil, Caerphilly, Cardiff, Newport, Blaenau Gwent, Torfaen, Swansea, Bridgend, Neath Port Talbot and Monmouthshire. The population is 1.9 million, with the highest populations found in the coastal city areas of Cardiff (capital of Wales 354,000 inhabitants), Swansea (241,000) and Newport (147,000). The counties of Rhondda Cynon Taff (237,000), Merthyr Tydfil (59,000), Blaenau Gwent (70,000), Torfaen (91,000) and Caerphilly (180,000) cover a hilly area north of the coastal towns, with a strong industrial history but currently relatively high levels of socioeconomic deprivation [15,16]. The area is served by several hospitals and most provide neurology services. Cases requiring electrophysiology, and other specialist care are usually referred to the University Hospital of Wales in Cardiff.

Here we present the investigation of cases and associated results reported as at noon on 20 January 2016.

Methods

Case definition

A possible cluster case was defined as a hospitalised patient with either GBS or AFP, in a resident of South Wales, with onset of paralysis on or after 1 September 2015. A probable case was a possible case with investigations showing an axonal neuropathy or with predominant (earlier or more severe) facial weakness or ophthalmoplegia, or a child (under 16 years of age) with AFP. Onset dates refer to the onset of paralysis.

The possible case definition was used to identify cases for further investigation, as both AFP and GBS are rare and investigations required to classify them can take days or weeks to complete.

Laboratory investigations

Cases were clinically investigated with neuroimaging i.e. magnetic resonance imaging (MRI) and computed tomography (CT) scans, electrophysiological studies (nerve conduction and electromyography), and analysis of anti-ganglioside antibodies as appropriate.

Laboratory investigations included testing of stool, respiratory (throat and naso-pharyngeal swabs), cerebrospinal fluid (CSF) and serum samples for a variety of viral [17] and bacterial pathogens.

All respiratory samples were first screened using a panel of real-time reverse transcription (RT)-PCR assays targeting influenza A and B, respiratory syncytial virus (RSV)-A and -B, human metapneumovirus (hMPV), parainfluenza virus 1-4 and finally a duplex PCR targeting adenovirus and *M. pneumoniae*. A specific rhinovirus assay targeting the 5' untranslated region (UTR) of the *Picornaviridae* family was duplexed with the hMPV assay. To type EV-D68, a further specific assay was used on all samples positive in the EV assay as developed by the EV-D68 European study group [17].

CSF pleocytosis was defined as a white cell count greater than 5 cells per cubic millimetre. Whole blood and urine samples were screened for heavy metals and organophosphate exposure, the latter via a red cell cholinesterase test.

Epidemiological investigation

Cases were interviewed using a semi-structured questionnaire with open questions to assess recent illnesses, earlier medical history and underlying conditions, as well as environmental and other exposures.

To identify the background incidence of GBS in Wales, we searched routinely collected hospital admission data in Wales with a primary diagnosis of GBS based on the World Health Organization (WHO) International Statistical Classification of Diseases and Related Health Problems (ICD-10) classification G61.0 [18], over a 10-year period between 1 January 2004 and 31 December 2014.

Results

We identified 10 adults (eight probable, two possible cases) and four children (all probable cases) who met the case definition. Case locations are displayed in Figure 1; most adults lived in local authority areas to the north of the coastal cities in South Wales.

Table

Demographics, clinical and laboratory findings for cases in adult cluster of atypical Guillain-Barré syndrome and child cluster of acute flaccid paralysis, South Wales, United Kingdom, October 2015-January 2016 (n = 14)

Case no	Age group (years)	Sex	Neurological diagnosis	Predominant facial/eye symptoms[a]	Nerve conduction studies	Case category	Prodromal illness	CSF pleocytosis[b]	Stool PCR for enterovirus	Respiratory PCR for enterovirus	Respiratory PCR Other pathogens detected
Adult cluster											
1	40–49	M	Bifacial weakness	Yes	AMAN	Probable	RTI	No	ND	Neg	None
2	50–59	M	Bifacial weakness / GBS	Yes	AMAN	Probable	RTI	No	Neg	ND	*Haemophilus influenzae*, adenovirus, rhinovirus
3	30–39	M	Bifacial weakness / GBS	Yes	AMSAN	Probable	RTI	ND	ND	ND	Rhinovirus
4	60–69	M	Bifacial weakness / Ophthalmoplegia/ GBS	Yes	AMAN	Probable	RTI	Yes	ND	Neg	Influenza A
5	70+	M	Asymmetric leg weakness	No	AMAN	Probable	None	No	ND	ND	Negative
6	40–49	M	Bifacial weakness / ophthalmoplegia	Yes	ND	Probable	RTI	ND	ND	ND	None
7	20–29	M	Hand predominant GBS	No	AIDP	Possible	RTI	No	Neg	Neg	Adenovirus
8	30–39	M	GBS	No	AIDP	Possible	None	No	ND	ND	None
9	40–49	M	Bifacial weakness / GBS	Yes	ND	Probable	RTI	No	ND	NEG	None
10	70+	M	Bifacial weakness	Yes	ND	Probable	GI	No	ND	ND	None
Child cluster											
1	0–4	F	AFP	No	AMAN	Probable	RTI	Yes	EV-D68	Neg	None
2	0–4	M	Lower limb paralysis	No	ND	Probable	RTI	Yes	ECHO25	Neg	None
3	10–14	F	GBS	No	AMSAN	Probable	RTI	No	EV-D68	EV-D68	None
4	0–4	F	Bifacial weakness / ophthalmoplegia	Yes	ND	Probable	None	No	Neg	ND	None

AFP: acute flaccid paralysis; AMAN: acute motor axonal neuropathy; AMSAN: acute motor sensory axonal neuropathy; CSF: cerebrospinal fluid; ECHO 25: echovirus 25; EV: enterovirus; F: female: GBS: Guillain-Barré Syndrome; GI: gastrointestinal illness; M: male; Neg: negative; ND: not done; Pos: positive; RTI: respiratory tract infection.

[a]These are cases where facial weakness or ophthalmoplegia were present early in the illness, or were more severe than limb weakness.

[b]CSF pleocytosis was defined as more than 5 white cells per cubic millimetre.

Cases of enterovirus and echovirus 25 in children are highlighted in grey.`

All adult cases were male, with a median age of 45 years (range 24–77). The dates of onset of paralysis ranged from 29 October 2015 to 8 January 2016 (Figure 2).

Eight of the 10 adult cases had a prodromal illness consisting of respiratory tract manifestations including sore throats, lower and other upper respiratory tract symptoms and ear infections in seven, and diarrhoeal illness in one.

The four child cases all presented with AFP; one had prominent facial and eye symptoms. They were three females and one male, aged between 1 and 13 years, with three aged 2 years or younger. Three of four had a respiratory infection preceding onset of AFP. They resided in four local authority areas (Figure 1).

The Table summarises the clinical and microbiological features of the adult and child cases.

Neurological findings

Of the eight probable adult cases, seven presented with prominent, mainly asymmetric facial weakness. One (Case 5) had predominantly lower limb weakness and an AMAN pattern on electrophysiology. In five of the eight cases nerve conduction studies were typical for AMAN or AMSAN. Case 5 was the only immunosuppressed individual (taking 50mg oral prednisolone per day); he presented with an acute asymmetric lower limb paralysis and electrophysiologically diagnosis was AMAN. Ophthalmoplegia was only a feature in one possible case who had a demyelinating pattern on electrophysiology.

The possible Cases 7 and 8 were more consistent with classical GBS, presenting with ascending or peripheral

weakness; both had electrophysiology consistent with Acute Inflammatory Demyelinating Polyneuropathy (AIDP).

All eight probable cases received immunoglobulin and seven of them had either a good or excellent response to it. Two cases (Cases 2 and 6) had positive titres to anti-GQ1b antibodies.

Three adults had spinal MRIs (Cases 10, 11 and 12), with no abnormalities detected; five had a cranial CT or MRI, with no evidence of a cause for the acute illness.

Three of the four children presented with an AFP; one of them with marked weakness of lower limbs only. The other child presented with an AFP with ophthalmoplegia and prominent facial weakness. Two had evidence of signal change on cervical spine MRI in keeping with a transverse myelitis (Cases 1 and 2).

Microbiological and toxicological investigations

Only one adult had a CSF leucocytosis (WBC 53); this case did not meet the criteria for a probable case. The clinical picture involved a complex and progressive ophthalmoplegia and asymmetric facial diplegia and the putative diagnosis of Bickerstaff's encephalitis was made. Results of PCR tests on respiratory samples from all 10 adult cases were positive for rhinovirus or adenovirus in two cases, respectively, one sample was positive for influenza and *Haemophilus influenzae* was identified by sputum culture in one case, which also tested positive for rhinovirus and adenovirus (PCR, included in above results). Two adults were tested for hepatitis B and C and one for hepatitis E; all were negative. Stool culture was performed in three of the adult cases and was negative in all of them.

Two children had white cells in their CSF, one was predominantly lymphocytic. Three of the four children had real-time RT-PCR evidence of EV in stool samples, of which two were typed as EV-D68 and the third had an echovirus 25; one child who was EV-D68-positive in stool also had a respiratory sample positive for EV-D68. One also had evidence of infection with *M. pneumoniae* by respiratory real-time RT-PCR and serology.

Biochemistry results were reported for four adult cases. Tests for heavy metals in whole blood confirmed no abnormalities in all of them. Six adults were tested for organophosphate exposure: one showed no abnormalities and five are still awaiting results.

Environmental exposures

All 10 adult cases were interviewed. Exposures reported more than once included contact with dogs (4/10) and other pets (2/10); tattoos (4/10); smoking (2/10, of those 1 e-cigarettes) and clay pigeon shooting (2/10). Two had travelled outside the United Kingdom (UK) in the two months before onset of illness to Spain and Bulgaria, respectively. None had travelled to an area reported to have had cases of Zika virus. None had had any recent vaccinations, including seasonal influenza vaccine, and none reported use of illicit substances, significant changes in medication or use of alternative medicines.

The four child cases were all age-appropriately vaccinated and none had had recent medication changes or exposure to toxic household chemicals; three had exposure to dogs or cats, and one had household exposure to a smoker. None had travelled outside the UK in the two months before onset of illness.

Excluded case

In addition to the four cases presented above, a further child in Wales had AFP with ophthalmoplegia and evidence of EV-D68 in stool samples during the same period, and was investigated as part of the cluster. However, they were excluded as they fell outside the area included in the initial case definition.

Hospital admissions data 2004–14

There were an average of 69 (range 49–91) admissions with GBS per year, an average of six (range 0–13) admissions per month. Admissions showed a seasonal pattern with the greatest number of admissions occurring in January (data not shown).

The background incidence of GBS in Europe is 1.2 to 1.9 per 100,000 [19], which would equate to around 36 to 58 cases per year, or three to five cases per month for all Wales (population 3.07 million [16]).

Discussion

The adult and child cases presented are clustered in both space and time, with adult cases showing predominantly the more unusual variant forms of GBS. The majority of adult cases showed AMAN and AMSAN i.e. features of the axonal variants of GBS. These variants are rare in Europe and the United States, where they account for only 5% of GBS cases. However, they are more common in China, Japan and Central and South America where they constitute 30–47% of cases [19]. None of our cases meet the diagnostic criteria for MFS [1], which has a much lower incidence than GBS (0.1/100,000 compared with 1.2–1.9/100,000 [19]).

This cluster of 10 adult cases over a three-month period would constitute a winter peak within the context of population estimates and hospital episode data for the past decade. What is unusual, compared with expected winter peaks of incidence, are the clinical features of facial weakness and asymmetric onset, and electrophysiological features of axonal involvement. The strong male predominance (all adults were male) is also unusual, with the usual male:female ratio estimated at 1.5:1 [19].

Both adult and child cases cluster geographically outside major cities, with 12 of 14 living outside the three main cities in the area (Cardiff, Newport and Swansea),

despite 48% of the population of the counties with cases being in these cities [16].

The child cases in our cluster are clinically different from the cases in the adult cluster, presenting with a syndrome similar to that previously reported for EV-D68 associated AFP, with half having radiological evidence of a transverse myelitis. Adult AFP cases have been reported coincident with a rise in EV-D68 cases [14], but in this series child cases predominated, with only nine of 59 cases aged over 21 years. Twelve children in Colorado had a neurological illness at a median of seven days following a febrile infection, with EV-D68 detected in five of 11 tested [20]. Their symptoms were flaccid limb weakness in 10 cases, bulbar weakness in six and two had facial weakness, accompanied by spinal MRI changes.

There is no clear hypothesis as yet for the cause of the adult cluster. The temporal association of the two clusters could represent a coincidence, or an artefact due to changes in local diagnosis. Current hypotheses under investigation include enterovirus infection, either EV-D68 or other types; gastrointestinal infections such as *Campylobacter* spp., hepatitis E infection and influenza. Variant forms of GBS have been associated with *C. jejuni* [3], but here there is no stool culture evidence of campylobacteriosis. Emerging arbovirus infections such as Zika and West Nile virus are unlikely as causes for the neurological symptoms due to the absence of suitable vectors in Wales and any appropriate travel history. The clinical picture of cases was not consistent with botulism.

Descriptive epidemiology, with predominance of adult males and some geographic clustering, might suggest an environmental or behavioural exposure. However, no common exposure supporting this theory has been identified and no evidence of toxic causes has been found from clinical samples so far.

All but four of the cases had a preceding respiratory tract infection. Influenza was first reported as circulating in Wales from week 1 in 2016 [21], post-dating the illness for these cases. Respiratory samples are not routinely tested for enterovirus, but retrospective PCR testing of respiratory samples from children (under 16 years of age) taken from 1 December to 6 January, found 17 of 163 with evidence of enterovirus and five of 17 with EV-D68.

The methods used in defining the clusters have limitations, mainly in keeping with an evolving early report. Not all cases have undergone the same level of neuroimaging, electrophysiological and microbiological testing, so the cases are defined mainly by their clinical presentation. Exposures have not yet been systematically obtained using a standardised, closed-question questionnaire. A further review, including more intensive case finding, is being undertaken to better characterise the cluster.

The child cases result either from increased recognition and diagnosis or increased true incidence of neurological disease caused by infection with EV-D68. Neurological illness due to EV-D68 has not previously been described in Wales. The adult and child clusters may be completely separate, but are presented together here because of their temporal association, and because EV-D68 neurological illness is a relatively rare diagnosis in the UK, although EV-D68 is thought likely to be circulating in the community [22].

Further investigations planned include serology for hepatitis E, influenza and other possible infection triggers, using stored serum and new samples to be taken after the intravenous immunoglobulins have left the patients' serum. Further antiganglioside antibody testing, and human leukocyte antigen (HLA) typing are also planned. Surveillance for atypical GBS continues in Wales using a standardised reporting form and following case finding alerts to clinicians, and enhanced surveillance for enterovirus infection is also planned. Public Health Wales has alerted clinicians, and has been working with Public Health England and the European Centre for Disease Prevention and Control (ECDC) to inform other European Union countries about this cluster via the Early Warning and Response System (EWRS).

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Conflict of interest

None declared.

Authors' contributions

RHT and TPP: Identifying cases, clinical description of cases;

CJW: Descriptive epidemiology, background and epidemiological methods;

GL: Principal investigator for the clusters;

ML: Managerial oversight and hypothesis generation;

HB: Biological sampling of environmental hazard exposures – methods and results;

RhES: Case exposure history ascertainment, questionnaire data collation, laboratory, clinical and toxicology liaison;

BWM: Conceived need for work, critically revised content for important intellectual content, approved final version;

CM, RJ, RH: Microbiological advice and specialist testing;

AA: Article conception as part of communications strategy.

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